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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/791,240	01/30/97	RYNCARZ	A	BDI-1020

HM12/0216

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EXAMINER	
SISSON, B	
ART UNIT	**PAPER NUMBER**
1655	28

DATE MAILED: 02/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/791,240	Alexander J. Ryncarz
Examiner	**Group Art Unit**
Bradley L. Sisson	1655

☒ Responsive to communication(s) filed on *18 Jun 1999*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-57 and 59-65* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-57 and 59-65* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Oath/Declaration

1. The objection to the oath or declaration has been withdrawn.

Specification

2. The disclosure is objected to because of the following informalities: The specification continues to contain numerous references to US Patent applications whose status has changed yet is not so indicated.

Applicant is requested to review the complete application for such instances and to update where needed.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-57 and 59-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The method of claim 1 requires the presence of but one primer, yet requires one to make copies of a primer extension product seemingly using the same primer. The specification does not reasonably provide enablement for making copies of primer extension reaction products when but a single primer is present. The specification also does not provide an enabling disclosure whereby any type of "controlled" condition for elongating a primer that had a 3'-mismatch.

Claims 2-57 and 59-65 are not enabled by the specification for the amplification of any target nucleic acid wherein said method one also incorporates an internal control whose nucleotide residue sequence is such that it results in a 3'-mismatch on a primer that anneals thereto. Neither the written description nor the claims recite the conditions nor steps required for the detection of point mutations where one would obtain but a single nucleotide extension to a primer annealed to the target yet would remain unchanged after the use of 3'-5' exonuclease. Further, the method does not set forth a repeatable procedure where one is to perform multiplex PCR and a 3'-5' exonuclease is used while in the presence of a variety of primers. The very presence of a 3'-5' exonuclease in a sample will result in the degradation of primer(s), template, internal control, as well as any amplification product.

It is well known in the art that hybridization and amplification reactions can and do incorporate the use of an array of primers or probes wherein said primers and/or probes are immobilized on the surface of a solid support. The claimed method encompasses such embodiments. The specification fails to address in sufficient detail how one would be able to eliminate only the 3' terminal residues of a mismatched primer to a internal control when the same exonuclease can degrade the primers/probes on the surface of a array device, thereby allowing for the elongation of

non-target sequences and the creation of conditions whereby primers previously non-complementary to a non-target sequence in the solution now become sufficiently complementary so to permit annealing and primer extension. As disclosed by Sommer and Tautz, weak priming was achieved with as little as two 3' bases being complementary while successful priming was achieved in primers of 17-22 nucleotides in length where there were but 3 residues complementary. In view of the art recognizing this sensitivity to priming with a tremendous level of non-complementarity between the primer and target, the use of an exonuclease on a mixture of primers may well result in the amplification of the internal control, but would also result in the amplification f innumerable non-target sequences as well. The specification has not provided a reproducible method whereby one would be able to prohibit such unwanted primer elongation and to differentiate between desired and non-desired product(s).

In order to practice the claimed method to the fullest extent of the claims' scope, the ordinary artisan would have to resort to the testing and evaluation of innumerable conditions and parameters with little, if any, reasonable expectation of success. Further, the claimed invention relates directly to matters of physiology and chemistry which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
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> *****
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> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

While argument has been presented that polymerase chain reaction is well known in the art, and there is no need for additional guidance, the record does not reflect that the use of a 3'-5' exonuclease in a PCR reaction was well known in the art, especially when this enzyme has the capacity to destroy the amplified target, any primers as well as the positive control. Accordingly, the state of the prior art does not reflect that this modification to the conditions is routine. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained and has been broadened so to encompass newly added claims.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. from 5 p.m. to Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-7230.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

B. L. Sisson

BRADLEY L. SISSON
PRIMARY EXAMINER
GROUP ~~1800~~ 1650
2/14/00